Impacts of mitochondrial-targeted antioxidant on leg function, leg blood flow and skeletal muscle mitochondrial function in peripheral artery disease patients

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DATA SAFETY MONITORING PLAN

Overall Framework for Safety Monitoring

During this study, limited personal information, including age, sex, body mass and height, will be collected from the subject. Research material that will be obtained from human subjects will be behavioral (i.e., walking distance and time, and data from the motion capture system). All collected data will be obtained from human subjects and used for research purposes only. Each subject will be assigned a study code upon enrollment. The subject code will be used to identify all data collected in the study. A listing of subject codes and names will be stored in a locked file room along with the subjects' signed informed consent documents. Only essential and authorized study personnel will have access to the subject code assignments. These data can be provided to the participant in de-identified paper or electronic form. A member of the research team will enter these data into an electronic database and store the paper copy of the results in a locked cabinet within the laboratory. The electronic database will be stored on password-protected computers that are secured behind the University of Nebraska at Omaha firewall system. They will be stored on encrypted hard drives that are kept in a locked cabinet within the laboratory. Only the PI and research team will have access to these data. Data that is recorded and stored for use in data analysis do not include any of the 18 HIPPA identifiers. The PI will assure that informed consent is obtained prior to performing any research procedures, that all subjects meet eligibility criteria, and that the study is conducted according to the IRB-approved research plan. Study data are accessible at all times to the PI and the Co-investigator to review. The PI will review study conduct accrual, drop-outs, and protocol deviations on a semi-annual basis. The PI and Co-investigators will review Adverse Events (AEs) individually and in aggregate on a semiannual basis. The PI and co-investigators will review serious adverse events (SAEs) in real-time. The PI ensures all protocol deviations, AEs, and SAEs will be reported to the NIH and IRB according to the applicable regulatory requirements.

Adverse Event and Serious Adverse Event Information

Definition

An adverse event (AE) is any untoward medical occurrence in a subject during participation in the clinical study or with use of the device being studied.

A serious adverse event (SAE) is any AE that results in one or more of the following outcomes:

- Death
- A life-threatening event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly or birth defect
- An important medical event based upon appropriate medical judgment

Classification of AE Severity

AEs will be labeled according to severity, which is based on their impact on the patient. An AE will be termed "mild" if it does not have a major impact on the patient, "moderate" if it causes the patient some minor inconvenience, and "severe" if it causes a substantial disruption to the patient's well-being.

AE Attribution Scale

AEs will be categorized according to the likelihood that they are related to the study intervention. Specifically, they will be labeled "definitely unrelated", "definitely related", "probably related", or "possibly related" to the study intervention.

AE Reporting and Follow-up

AEs will be recorded by members of the research team following the incident.

AEs that are unanticipated, serious or fatal, and possibly related to the study intervention will be reported to the IRB and the NIH within 7 days.

Other serious and unexpected AEs related to the intervention will be reported to the IRB and NIH within 15 days.

Any other unanticipated problem will be reported to the IRB within 15 days of the investigator becoming aware of the problem.

Anticipated or unrelated SAEs will be handled in a less urgent manner but will be reported to the IRB and NIH within one month.
All unanticipated problems will be reported to the appropriate institutional officials and the NIH Program Officer within one month of the IRB's receipt of the report of the problem from the PI.

AE Attribution Scale
AEs will be categorized according to the likelihood that they are related to the study intervention. Specifically, they will be labeled definitely unrelated, definitely related, probably related, or possibly related to the study intervention.

Description of Plan for Data Quality and Management
The PI will review all data collection forms on an ongoing basis for data completeness, accuracy and protocol compliance.
The PI will be meeting with personnel involved in data collection on a weekly basis. During this time, all data monitoring will be performed.
The PI will become informed on enrollment, consent of individuals, data collections, data reduction and data analysis. He will require that he sees raw data and will oversee all procedures to ensure they are being properly followed.
If any issues arise, such as an adverse event or complaint, the PI will complete the required report forms and submit them to the IRB.

Annual progress reports, including patient recruitment, retention/attrition, and AEs, will be provided to the NIH. In addition, the Annual Report will address (1) whether AE rates are consistent with pre-study assumptions; (2) reason for dropouts from the study; (3) whether all participants met the entry criteria; (4) whether continuation of the study is justified on the basis that additional data are needed to accomplish the stated aims of the study; and (5) conditions whereby the study may be prematurely terminated. The Annual Report will be sent to the SO and will be forwarded to the IRB and NIH. The IRB and other applicable recipients will review the progress of this study on an annual basis.

Frequency of Data and Safety Monitoring
The frequency of data review for this study differs according to the type of data and is summarized in the following table:

Data Type	**Frequency of Review**	**Reviewer**
Status of all enrolled subjects	Quarterly	PI
AEs and rates	Quarterly	PI
SAEs	Per occurrence	PI, NIH
Raw data integrity	Weekly	PI
Processed data integrity	Monthly	PI